Mycobacterial Diseases

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Abstract

Cats may be infected with a variety of both rapidly- and slowly-growing mycobacterial species, which cause a variety of clinical syndromes in cats, from localized skin disease to disseminated and potentially fatal infections. Cutaneous disease is the most common manifestation for all causative species; however, some species may have internal involvement, with any organ system, skeletal or soft tissue structure potentially infected. Infections by rapidly-growing mycobacteria generally result in fistulating panniculitis of the inguinal region or less commonly, axillae, flanks or dorsum, whereas those caused by members of the slow-growing taxons typically present with solitary or multiple nodular skin lesions and/or local lymphadenopathy, especially of the head, neck and/or limbs. Most affected cats do not appear to have an underlying immunosuppressive condition, and no association has been made with a positive retroviral status. Most cases occur in adult cats with unrestricted outdoor access. Depending on the causative species and the extent of disease when first diagnosed, these infections can be challenging to treat. Generally, localized cutaneous infection caused by all species has a relatively favorable prognosis if treated with an appropriate combination of drugs and surgery, if necessary. If the cat acquires systemic infection, the prognosis becomes significantly worse. The commitment of the owner to the implementation of a potentially expensive and time-consuming schedule of multidrug therapy for many months may also influence the outcome. The zoonotic potential of these organisms is generally low, however cat-to-human transfer of *Mycobacterium bovis* has been reported.

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Mycobacteria are aerobic, nonmotile, Gram-positive, nonspore-forming bacilli in the phylum *Actinobacteria*. Of the more than 180 mycobacterial species identified [1], almost all are environmental saprophytes. However, a few, such as the *Mycobacterium tuberculosis* complex (MTB), *M. leprae* and its relatives, members of the *M. avium* complex (MAC), such as *M. avium* subsp. *paratuberculosis* and *M. lepraemurium*, appear to have evolved into obligate pathogens.

Mycobacterial species can be divided genetically and phenotypically into two main groups: rapidly growing (RGM) and slowly growing mycobacteria (SGM). The RGM are ancestral to the SGM, with the latter forming a distinct genetic subbranch based on analysis of housekeeping genes and, more recently, whole-genome analysis [2]. The *M. abscessus/chelonae* complex appears to be the genetically oldest group identified, with *M. triviale* and also the closely related *M. terrae* group the likely evolutionary links between the RGM and the SGM [2].

Mycobacterial infections cause a variety of clinical syndromes in cats, from minor localized skin disease to potentially fatal disseminated infections. Cutaneous disease is the most common manifestation for all causative species; however, some species, particularly the MTB and MAC, may have internal involvement with any organ system, skeletal or soft tissue structure, potentially infected.

Few investigations have examined substantial cohorts of cats with mycobacteriosis and only some definitively identified the causative mycobacterial species via genetic analysis. These studies are typically limited to animals from a particular geographical region and may not be representative of the disease in cats domiciled elsewhere, especially with regard to incidence and causative species.

Typically, cats with mycobacterial infections do not appear to have an immunosuppression, and no association has been made with a positive retroviral status, unlike MAC infections in people with human immunodeficiency virus/acquired immunodeficiency syndrome. Regardless of the causative species, most cases occur in adult cats with unrestricted outdoor access, although MAC infections have been occasionally reported in exclusively indoor cats.

Rapidly Growing Mycobacteria

Etiology and Epidemiology

The RGM are environmental saprophytes widely distributed as free-living organisms in both terrestrial and aquatic biomes. The RGM are so named as they are able to grow on synthetic culture media within 7 days at 75–113° F (24–45° C).

RGM have low inherent pathogenicity and generally tend to cause opportunistic infections in cats, mostly through breaches in the integument, for example, via cat-scratch wounds. They have a low tendency to cause systemic disease unless the host is immunocompromised, although occasionally inhalation of organisms may lead to pneumonia in apparently immunocompetent individuals. The disease manifests in cats primarily as ventral abdominal panniculitis and tends to be caused by the *M. smegmatis*, *M. margaritense*, *M. fortuitum*, and *M. chelonae-abscessus* groups.

Cases are reported from the Americas (Brazil, southeastern and southwestern United States, Canada), Oceania (Australia and New Zealand), and Europe (Finland, the Netherlands, Germany, and the United Kingdom). The incidence of particular causative organisms varies between geographical regions. *M. smegmatis* and *M. margaritense*, followed by *M. fortuitum* groups, cause most infections in cats in eastern Australia, whereas, in the southwestern United States, *M. fortuitum* group followed by *M. chelonae* infections appear to be more common.

Cats with a prominent ventral abdominal fat pad appear to have a predisposition toward RGM infection. This is likely due to the preference of the organisms for tissues rich in lipid, which may provide triglycerides for growth and perhaps protection from the host immune response. In cats that do not have a significant amount of subcutaneous fat, the ability to establish experimental infections appears to be limited [3].

Clinical Features

Typically, lesions caused by RGM are located in the inguinal region or, less commonly, axillae, flanks, or dorsum. Initially, the infection appears as a circumscribed plaque or nodule of the skin and subcutis. Subsequently, the affected cat develops alopecic areas of thin epidermis which overlies and is adherent to diseased subcutaneous tissue; this results in a characteristic "pepper pot" appearance (Fig. 1). The characteristic focal purple depressions in the skin break down to become fistulae exuding a watery discharge that may become purulent with secondary infection. The lesions may eventually involve the entire ventral abdomen, flanks, perineum, and occasionally the limbs. Internal organs or lymph node involvement is not likely; however, the abdominal wall is rarely involved.

Most cats do not have signs of systemic illness unless the skin lesions become secondarily infected with *Staphylococcus* and *Streptococcus* spp., in which case the patient may display lethargy, pyrexia, anorexia, weight loss, and reluctance to move.

Diagnosis

Fine needle aspiration and cytology may establish the presence of pyogranulomatous inflammation, and subcutaneous exudate may be obtained with this technique to allow the culture of the organism, thus establishing the diagnosis.

RGM are not typically visible on either Romanowsky-stained cytological samples or hematoxylin and eosin-stained histopathology sections of biopsy tissue. Instead, they are visualized using acid-fast stains, such as Ziehl-Neelsen (ZN) or Fite's.

RGM may be few in number and difficult to visualize in acid-fast stained cytological material, and the diagnosis is not excluded if organisms are not visualized. The organisms may be lost during processing of cytologic and histopathologic

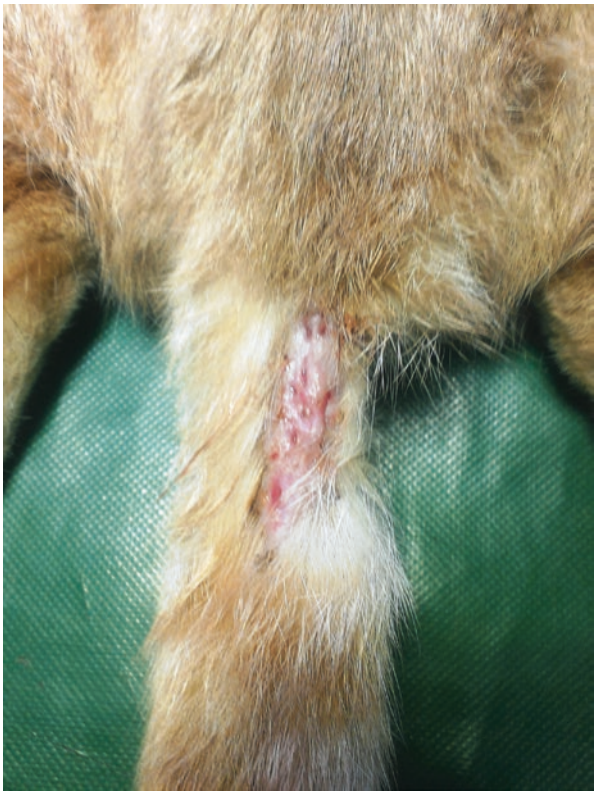

Fig. 1 The typical appearance of dermatitis/panniculitis caused by a rapidly growing mycobacterial species, *Mycobacterium smegmatis*. (Courtesy of Nicola Colombo)

samples as they tend to exist extracellularly in fat vacuoles in tissues. Occasionally, positive results on mycobacterial culture or molecular methods such as polymerase chain reaction (PCR) may be obtained on samples that are "acid-fast bacilli (AFB)-negative" on cyto- or histopathological evaluation.

Punch biopsies of the skin are usually inadequate for obtaining representative tissue samples, and a deep subcutaneous tissue biopsy from the margin of the lesion is preferred. The histopathologic characteristics of RGM dermatitis/panniculitis include an ulcerated or acanthotic dermis overlying multifocal to diffuse pyogranulomatous inflammation, which tends to extend well into the subcutis. In the pyogranulomas, a rim of neutrophils often surrounds a clear, inner zone of degenerate adipocytes, which may contain scant AFB with an outer collection of epithelioid macrophages (Fig. 2). A mixed inflammatory response, predominantly comprising neutrophils and macrophages, but also containing lymphocytes and plasma cells, is found between each pyogranuloma. AFB may also occasionally be visualized within macrophages but can be very hard to find within tissue sections.

When attempting to culture mycobacteria from panniculitis lesions, material swabbed directly from cutaneous draining sinus tracts usually contains high numbers of contaminating skin bacteria, which outcompete the RGM on culture media.

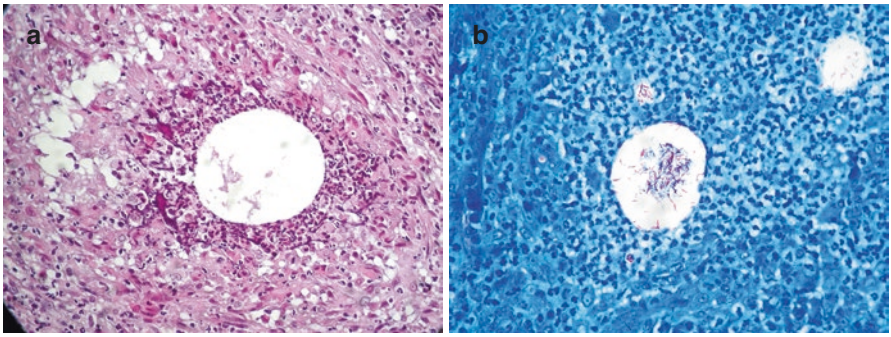

Fig. 2 (**a**) Histopathological aspect of rapidly growing mycobacterial infection: pyogranulomatous inflammation with a rim of neutrophils surrounding a clear, inner zone of degenerate adipocytes, which contain acid fast bacteria (H&E 400×); (**b**) Ziehl-Neelsen stain of the same sample: rod shaped bacteria are stained in red and can be easily recognised (400×). (Courtesy of Dr. Chiara Noli)

Fine-needle samples obtained through intact skin decontaminated with 70% ethanol or surgically collected subcutaneous tissue biopsies are therefore preferred. Uncontaminated samples of RGM grow readily on routine media such as blood [4] and MacConkey agar (without crystal violet), so there is usually no need for the clinician to request "mycobacterial media" culture for these organisms specifically.

Treatment and Prognosis

Depending on the causative species and the extent of disease when first diagnosed, these infections can be challenging to treat. They often have a high rate of recurrence, frequently require protracted courses of therapy, and may have a substantial incidence of inherent and/or acquired drug resistance.

Susceptibility data is especially useful for organisms that may have inherently variable drug susceptibility, such as *M. fortuitum*, or for recurrent or chronically persistent RGM infections, especially where the cat has undergone prior antibiotic treatment which may have induced acquired drug resistance. Ideally, treatment should begin with one or two oral antimicrobials (doxycycline, a fluoroquinolone, and/or clarithromycin). These are usually chosen empirically until results of culture and susceptibilities are known. In Australia, doxycycline and/or a fluoroquinolone – preferably pradofloxacin – are best, whereas, in the United States, clarithromycin is the drug of choice initially. *M. smegmatis* group tends to be inherently resistant to clarithromycin, and some isolates may be resistant to the enrofloxacin or ciprofloxacin, although this does not rule out susceptibility to pradofloxacin [5]. Members of the *M. fortuitum* group are typically susceptible to fluoroquinolones, however, demonstrate variable expression of the erythromycin-inducible methylase (*erm*) gene which confers macrolide resistance [6]. Approximately 50% of *M. fortuitum* isolates are susceptible to doxycycline [7]. *M. chelonae-abscessus* group isolates tend to be resistant to all drugs available for oral dosing apart from clarithromycin and

linezolid. Where indicated by drug susceptibility data, refractory cases may be treated with clofazimine, amikacin, cefoxitin, or linezolid. It is recommended to commence treatment at standard dose rates increased slowly to the high end of the dose range, unless adverse effects are observed.

Treatment duration is variable, but it is recommended to continue therapy for 1–2 months past resolution of all clinical signs. Some animals with recalcitrant lesions benefit from en bloc resection of isolated areas of infection, often necessitating reconstructive surgery [8] or vacuum-assisted wound closure [9, 10].

Public Health Risks

Zoonotic transmission of RGM organisms from infected animals to humans is very unlikely. There is one report of *M. fortuitum* infection in an otherwise healthy middle-aged woman, after a cat bite to the forearm [11].

Slowly Growing Mycobacteria

The SGM taxon includes a large number of opportunistic environmental species: the obligate pathogens, *M. leprae* and *M. lepromatosis*, and the members of the *M. tuberculosis* complex. There are also a number of fastidious species included – traditionally classified as the causative species of "feline leprosy" – that are incapable of growing in axenic culture; thus, their epidemiological niche is unclear.

Tuberculous Mycobacteria

Cats are naturally resistant to *M. tuberculosis*, but occasional infections likely transmitted directly from humans are reported [12]. Disease in cats is most commonly caused by *M. bovis* and *M. microti* [13]. *M. bovis* has worldwide endemicity. However, much of Continental Europe, parts of the Caribbean, and Australia are free of the disease due to widespread surveillance, slaughter of test-positive cattle, the pasteurization of milk, and the absence of a wildlife host. *M. microti* is endemic to Europe and the United Kingdom (UK). Its main reservoir appears to be voles, shrews, wood mice, and other small rodents [14].

The exact route of transmission of these MTB species to cats is unclear. Numerous potential rodent prey species collected from areas of southwest England were found to be infected with *M. bovis* [15]. Suspected nosocomial contamination of surgical wounds has been reported [16].

MAC and Other Slowly Growing Saprophytes

Disease in cats is caused by several saprophytic slowly growing mycobacterial species, mostly members of the MAC, which are found worldwide in water sources and soil. Certain slowly growing species are more common in some environmental

niches or particular geographical areas, for example, *M. malmoense* or biofilms with *M. intracellulare* in the UK and Sweden. Some have highly restricted, focal areas of endemicity, for example, *M. ulcerans* infection.

As with MTB complex, the clinical picture is determined by the route of infection. Cats likely acquire skin lesions via transcutaneous inoculation of contaminated environmental material. Most cats with slow-growing mycobacterial infections have unrestricted outdoor access, and almost all of these cases had no overt predisposing conditions.

Fastidious Mycobacteria

"Feline leprosy" has been diagnosed in New Zealand, Australia, western Canada, the UK, southwestern United States, continental Europe, New Caledonia, the Greek islands, and Japan. Historically, New Zealand and Australia have reported the highest number of cases worldwide.

Genetic studies have identified the involvement of several "non-culturable" species of mycobacteria: *M. lepraemurium*, *Candidatus* "M. tarwinense,' [17, 18] *Candidatus* "M. lepraefelis,' [19] and *M. visibilis*, although the latter has not been reported for many years [20]. *M. lepraemurium* tends to cause disease in young male cats, whereas *Candidatus* "M. tarwinense" and *Candidatus* "M. lepraefelis" are more likely to cause disease in middle-aged to older cats. There is no gender preponderance for *Candidatus* "M. tarwinense" infection, whereas *Candidatus* "M. lepraefelis" is slightly more likely to cause disease in males.

Clinical Features

The majority of cats with SGM infection have solitary or multiple nodular skin lesions and/or local lymphadenopathy, especially of the head, neck, and/or limbs (Fig. 3). Ulceration of cutaneous lesions and the skin overlying affected lymph nodes may be

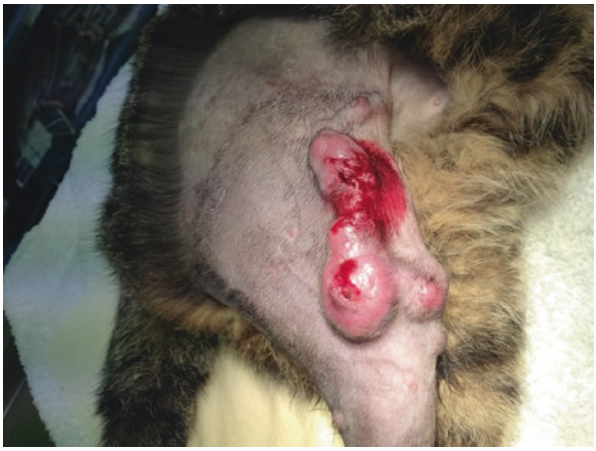

Fig. 3 Large, ulcerated nodules on the lateral thigh of a young male cat with *Mycobacterium lepraemurium* infection. Despite the widespread nature of the cutaneous lesions, this cat was cured with multidrug therapy including rifampicin and clofazimine. (Courtesy of Dr. Mei Sae Zhong)

observed, and infection may occasionally involve contiguous muscle and bone, which is more often the case with MTB complex species than other causative agents. In some cases, the dermal lesions may be widespread, involving many cutaneous sites. Host factors (age, concurrent illness, immunological status), the causal species, or the route and size of the inoculum may influence the nature of the disease.

If systemic disease is detected, the most common causative agents are either the MTB complex mycobacteria (especially in the UK and New Zealand) or members of the MAC. Rarely, systemic infections by other mycobacterial species, including other slowly growing saprophytes and *Candidatus* "M. lepraefelis," have been documented.

Diagnosis

Differential diagnoses of nodular skin and subcutaneous lesions include *Nocardia* and *Rhodococcus* spp. (which may also be acid-fast), fungi, or algal infections and primary or metastatic neoplasia. There are no pathognomonic clinical features that differentiate mycobacterial infections from other etiologies, and collection of representative tissue samples for cytology or histopathology and microbiology is necessary for the diagnosis.

It is vital in areas endemic for the MTB complex that the diagnosis is not based simply on cytologic or histopathologic findings. An attempt to identify the causative agent should be made in every case, ideally via a mycobacterium reference laboratory or equivalent, especially where mandatory reporting of such cases may result in compulsory euthanasia.

The diagnosis of cutaneous infections caused by SGM is often relatively simple, provided there is a high index of suspicion. Personal protective equipment should be worn during any procedure which involves handling of discharging or ulcerated lesions and/or surgical or necropsy tissues, when members of the MTB complex are a possible cause of disease.

Ideally, at the time of biopsy sampling for histopathology, a piece of fresh tissue wrapped in sterile saline-moistened gauze swabs placed in a sterile container should be collected, if microbiological processing is needed. The pathology laboratory should ideally be notified before submission, as SGM culture and identification requires specialized expertise.

Romanowsky-stained cytological samples of cutaneous nodules will demonstrate granulomatous to pyogranulomatous inflammation, and mycobacteria are recognized by their characteristic "negatively staining" appearance (Fig. 4), usually located within macrophages. As with the RGM, SGM are not typically visible on Romanowsky-stained cytological or hematoxylin and eosin-stained histopathology sections, except *M. visibile* and *Candidatus* "M. lepraefelis." Instead, Ziehl-Neelsen (ZN) staining (Fig. 5) or similar (e.g. Fite's) is required. Depending on mycobacterial species and host immune response, bacterial numbers may be variable.

MTB complex organisms produce characteristic solitary to coalescing granulomas ("tubercules"). Granulation tissue surrounds a layer of mixed inflammatory cells, consisting of macrophages, neutrophils, lymphocytes, and plasma cells. The

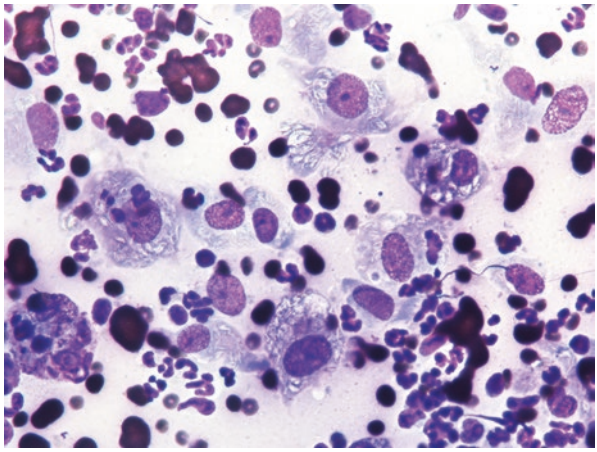

Fig. 4 Numerous macrophages with cytoplasm filled with many achromatic rod-shaped areas (Diff Quick, 1000×). (Courtesy of Dr. Francesco Albanese)

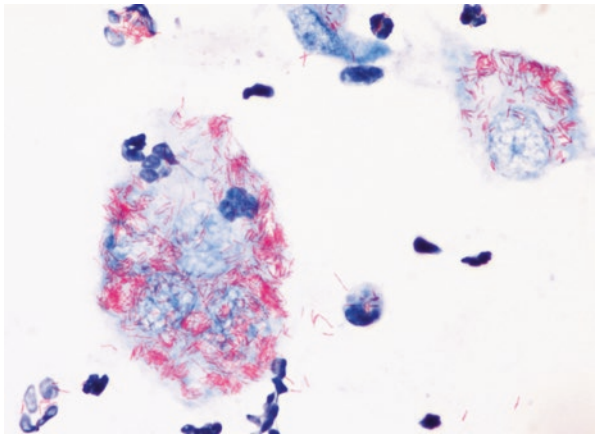

Fig. 5 Many brightly red and rod-shaped Mycobacteria are well recognizable with Ziehl-Neelsen staining (1000×). (Courtesy of Dr. Francesco Albanese)

center of the granuloma contains epithelioid macrophages and some neutrophils, with variable but usually low numbers of AFB, with or without necrotic tissue.

Cutaneous MAC infections cause pyogranulomatous or granulomatous inflammation with a variable fibroblastic response. The fibroblastic reaction may, on occasion, be so pronounced as to make it difficult to differentiate the disease from an inflamed fibrosarcoma (so-called "mycobacterial pseudotumor") [21]. AFB found both within macrophages and spindle cells identify the underlying etiology in these cases (Fig. 6). In the absence of a prominent fibroblastic response, lesions may resemble lepromatous leprosy.

The pathological picture of feline leprosy is subdivided into multi-bacillary (lepromatous) and pauci-bacillary (tuberculoid) forms [22]. "Multi-bacillary" leprosy is thought to correspond with a weak cell-mediated immune (CMI) response. Typically, many foamy or multinucleate macrophages, containing huge numbers of mycobacteria, are observed. There is no necrosis, and lesions contain virtually no lymphocytes and plasma cells. "Pauci-bacillary" leprosy, in which moderate to few

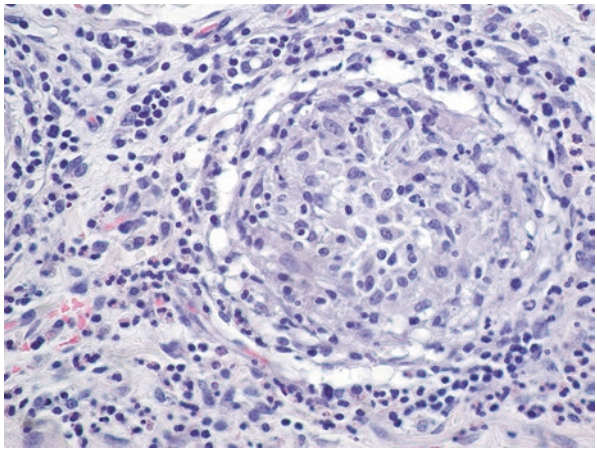

Fig. 6 Histopathological appearance of MTB complex infection: granulomas consisting of macrophages, neutrophils, lymphocytes and plasma cells. The center of the granuloma contains epithelioid macrophage (H&E 400×) (Courtesy of Dr. Chiara Noli)

observable AFB are found within pyogranulomatous inflammation dominated by epithelioid histiocytes, is thought to occur with a more effective CMI response. Moderate numbers of lymphocytes and plasma cells are also observed, with multifocal to coalescing necrosis. Involvement of peripheral nerves, a feature of human leprosy, is not seen in cats.

Except where samples have become contaminated with environmental mycobacteria, molecular methods, such as PCR and sequencing, can provide a highly accurate diagnosis on fresh or frozen tissue, formalin-fixed paraffin-embedded tissue sections, and Romanowsky-stained cytology slides [23]. It should be remembered that for samples in which no AFB are visualized microscopically, mycobacterial infections cannot be excluded with a negative PCR result.

A feline IFN-γ ELISPOT test is currently commercially available [24]. This test utilizes both bovine tuberculin and ESTAT6/CFP10 for the identification of cats infected with either *M. bovis* or *M. microti* and is able to differentiate the two mycobacteria. It is reported as having a sensitivity of 90% for detecting feline *M. bovis* infections, 83.3% sensitivity for detecting feline *M. microti* infections, and 100% specificity for both.

Serum antibody tests (multi-antigen print immune-assay (MAPIA), TB STAT-PAK, and Rapid DPP VetTB) have been evaluated in cats with TB [25]. Overall sensitivity was 90% for detection of *M. bovis* infection and greater than 40% for *M. microti*, with a specificity of 100%.

It is important to remember that these tests do not explicitly differentiate active from latent infection or prior exposure. Culture of organisms from clinical samples obtained from cats with appropriate signs and diagnostic findings remains the gold standard for the diagnosis of active TB.

Treatment

Controlled studies of feline mycobacteriosis treatment are lacking, and the existing literature consists of a few retrospective observational case series and case reports.

Table 1 Drugs typically chosen to treat feline mycobacterial infections

Drug	Dose	Side effects/comments
Clofazimine	25 mg/cat PO q 24 h or 50 mg/cat q 48 h	Skin and body fluid discoloration (pink-brown), photosensitization, pitting corneal lesions, nausea, vomiting, and abdominal pain Possible hepatotoxicity Monitor serum hepatic enzymes[a]
Clarithromycin	62.5 mg/cat PO q 12 h	Cutaneous erythema and edema, hepatotoxicity, diarrhea, and/or vomiting, neutropenia, thrombocytopenia
Azithromycin	5–15 mg/kg PO q 24 h	Vomiting, diarrhea, abdominal pain, hepatotoxicity
Rifampicin	10 mg/kg PO q 24 h	Hepatotoxicity and/or inappetence, cutaneous erythema/pruritus, anaphylaxis Monitor serum hepatic enzymes[a]
Doxycycline	5–10 mg/kg PO q 12 h	Hydrochloride or hyclate formulations may cause esophageal irritation and possibly stricture
Enrofloxacin Marbofloxacin Orbifloxacin	5 mg/kg PO q 24 h 2 mg/kg PO q 24 h 7.5 mg/kg PO q 24 h	Enrofloxacin may cause retinal toxicity in cats; marbofloxacin or orbifloxacin are preferred if available Most *M. avium* complex organisms are resistant to second-generation fluoroquinolones
Pradofloxacin	7.5 mg/kg PO q 24 h	Give without food unless gastrointestinal side effects occur
Moxifloxacin	10 mg/kg PO q 24 h	Vomiting and anorexia; dose can be divided 12 hourly and/or administered with food

[a]Alanine transferase and alkaline phosphatase

There have been occasional reports of spontaneous resolution of *M. lepraemurium* infection; [26, 27] however, the vast majority of SGM infections require treatment to achieve a cure. Table 1 lists the drugs and doses typically chosen to treat feline mycobacteriosis.

The initiation of empirical treatment is required in almost all cases of SGM infection, as identification of the causative mycobacterium may take weeks to months (or may not be available at all). The choice of initial treatment will depend on [1] the suspected etiological agent, [2] owner factors such as finances and ability/willingness to medicate the cat orally for an extended period, and [3] the presence of comorbidities that may restrict the use of certain drugs, for example, hepatic disease when using rifampicin.

Therapy should include at least rifampicin, clarithromycin (or azithromycin), and/or pradofloxacin (or moxifloxacin). In areas where infection with the fastidious organisms is common the inclusion of clofazimine, if available, would also be a reasonable choice. Ethambutol and isoniazid have been used to treat feline TB, although toxicity tends to limit their use. They tend only to be prescribed if there is drug resistance to the more commonly utilized agents. If the infection is restricted to a localized cutaneous site, surgical excision may be a beneficial adjunct to antibiotic therapy.

Medical treatment can be subsequently modified depending on identification of the mycobacterial species involved, response to treatment, and/or, if available, the

results of drug susceptibility testing. Therapy should extend for at least 2 months post-surgical resection or beyond resolution of clinical signs. Unless diagnosed with MTB complex infection, quarantine of the cat is not necessary. Some of the drugs, especially clofazimine, induce photosensitivity; it is recommended that owners keep the cat indoors in the summer months.

Prognosis

Localized cutaneous infection caused by all slowly growing species has a good prognosis if treated promptly with a combination of appropriate antibiotics, and if possible surgical resection. If cutaneous disease progresses to systemic infection, the prognosis becomes significantly worse. Treatment is potentially expensive and time-consuming. Cats can be notoriously tricky to medicate, and the provision of multidrug therapy for many months may also affect the outcome.

Public Health Risks

The only SGM that appears to carry a definite risk of cat-to-human transfer is *M. bovis*, although this risk seems to be low. A report from the UK details the infection in four people (two clinically and two sub-clinically affected) associated with an infected pet cat [28]. A laboratory worker seroconverted after exposure to research cats that were infected after accidentally being fed infected meat [29]. At this time, instances of cat-to-human transmission of *M. microti* infection have not been reported.

There is one report of a person contracting *M. marinum* secondary to a cat scratch [30]. However, this likely represented mechanical inoculation, rather than true zoonotic transfer. Likewise, there appears to be almost no risk of humans acquiring infections from any of the fastidious organisms from cats; however, as the ecology and transmission of these mycobacterial species are not understood, it is difficult to determine their potential for zoonotic transfer completely.

The Advisory Board on Cat Diseases (based in Europe) recommends that all people in contact with an infected cat should be made aware of the potential but low risk of zoonotic transfer of feline mycobacteriosis [31]. As a minimal precaution, the use of gloves is recommended when treating these animals. This is especially important for anyone in contact with the cat who is immunocompromised. Veterinary staff should utilize personal protective equipment when handling cats with cutaneous lesions, collecting biopsies, or performing necropsy studies.

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